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Date of mailing (day/month/year) 28 April 2000 (28.04.00)	
International application No. PCT/GR99/00030	**Applicant's or agent's file reference**
International filing date (day/month/year) 13 August 1999 (13.08.99)	**Priority date** (day/month/year) 14 August 1998 (14.08.98)
Applicant KAROUZAKIS, Petros et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

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(54) Title: USE OF MISOPROSTOL OR/AND MISOPROSTOL ACID FOR PREPARING DRUG IN ORDER TO CURE SEXUAL DYSFUNCTION IN WOMEN

(57) Abstract

Use of misoprostol or land misoprostol acid for preparing of a pharmaceutical product in order to cure sexual dysfunction in women. The invention relates to using an already known pharmaceutical substance, misoprostol or/and its first metabolite (misoprostol acid) whose structural formulas are presented in Annex (I) (Figures 1 & 2), for preparing a drug of external use destined to cure sexual dysfunction in women. Misoprostol or/and misoprostol acid according to the described method are applied externally to the clitoris or/and to the vagina, are absorbed and cause topical vasodilation resulting in the feeling of sexual desire in women suffering from sexual dysfunction, due to vascular or other causes. Simultaneously misoprostol promotes the coming of orgasm.

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USE OF MISOPROSTOL OR/AND MISOPROSTOL ACID FOR PREPARING DRUG IN ORDER TO CURE SEXUAL DYSFUNCTION IN WOMEN.

The invention relates to the use of an already known pharmaceutical substance, misoprostol as well as its first metabolite, misoprostol acid, for preparation of a drug for external use which is destined to cure sexual dysfunction in women.

The problem of the female sexual dysfunction even though it has been setted by the modern medicine decades ago, it hasn't been yet confronted with efficiency.
The extension of the problem is not quite known (Scrip Reports, March 1998), but according to an older research (Frank et al.,1978) the percentage of women facing a kind of dysfunction is going up to 63 %.

In our days the sexual dysfunction of women is being confronted either with surgical restoratoin, when -rarely- it has to do with anatomic problems, or with psychotherapy, that could be effective in cases where the causes are not functional, or even with the spesific treatment of substitution in cases where sexual inability has to do with hormonal disturbance.

These methods are being confronted with skeptikism, or because they are applying to a very small percentage of women (e.g.women with anatomic problems), either because they are characterized by a low efficiency, in accordance -many times- to an adverse relation between benefit and risk.
The interest of many searchers nowdays has been turned to the use of vasoactive substances, in accordance with the methods used in the treatment of male impotence. But these methods even though they are successfully used in men (for example intracavernosal injections), they strike against the female genital system

(inability of selfinjection into the corpora cavernosa of the clitoris), either the inefficiency of the methods that are for external use.

The present method aims at the removal of the disadvantages of the above methods with the use of a simple method, that consists of the local application of a vasoactive substance, known as misoprostol, to the clitoris or/and to the vagina, in order to cure sexual dysfunction in women due to vascular, hormonal, phychogenic or other cause.

Misoprostol is the general name of a synthetic prostaglandin belonging to the E_1 series (PGE_1 analogs). Synthesis:P.W.Collins,R.Pappo,Belgian patent 827.127, American patent 3.965.143 (The Merck Index,ed.Merck & Co. Inc,11th edition,1989,p.6128). Its chemical name is (11a,13E)-(±)-11,16-Dihydroxy-16-methyl-9-oxoprost-13-en-1-oic acid methyl ester or (±)-(methyl)-(1R,2R,3R)-3-hydroxy-2-[(E)-(4RS)-4-hydroxy-4-methyl-1-octenyl]-5-oxocyclopentaneheptanoate or (±)-15-deoxy-(16RS)-16-hydroxy-16-methyl-PGE_1 methyl ester.It is consisted of 4 stereoisomers in about equal proportions [(+)&(-) enantiomers of 16R- and 16S-forms].(The Merck Index, 11th edition, 1989,p.6128).The empirical formula is $C_{22}H_{38}O_5$.

Its structural formula appears in page 8, Fig.1.

Compared with other prostaglandins of group E_1 and especially alprostadil,misoprostol bears a methyl group (-CH_3) on the carbon atom of position 16.

According to a method which relates the biological action of various medicament molecules to its chemical structure it appears that due to this group we have a big penetration of misoprostol in the underlying tissues and a local vasodilation which cure sexual dysfunctions. Misoprostol is used today orally as antiulcer drug

(Physicians Desc Reference,PDR,ed.Medical Economics Data,Production Company at Montrale 48th edition,1994,P.2197-2199).

In particular it is administered for the prevention of gastric ulcer to patients who take non-steroid antiinflammatory drugs.It is available in the countries of Europe and U.S.A. by Searle Company under the commercial name Cytotec®.In none country is the drug mentioned as suitable for male impotence nor are there any relevant reports on the international bibliography.On a contrary amongst the undesirable effects in oral therapy with misoprostol is male impotence (Physicians Desc Reference, ed.Medical Economics Data,Production Company at Montrale,48th edition, 1994,p.2197-2199).

Misoprostol -compared to other vasodilatory drugs (e.g.nitroglycerin, Prostaglandin E_1 etc.)- cause a strong local vasodilation and as a result increase of the blood flow when it is used externally to the clitoris or/and to the vagina.Because of the local vasodilation is caused tumescence of the clitoris, intence bleeding of the vagina and feeling of sexual desire.Simultaneously, in women with anorgasmia of various causes, promote after masturbation or sexual intercourse, the coming of orgasm.

Equally strong topical vasodilation after external application is exerted by the hydrolysis product of misoprostol (misoprostol acid) which anyway constitutes the first misoprostol metabolite after its introduction in the organism (see page 8, Fig.2).

Last because of the intense topical vasodilatory action of misoprostol and the corresponding free acid.the two pharmaceutical molecules reinforce the absorption of other vasoactive substances (e.g.alprostadil) resulting in the occurrence of synergic action.

Misoprostol can be dissolved in water and its compatibility with excipients provides the opportunity of production of a variety of simple pharmacotechnical forms for external use, which are at the same time very well tolerated by the skin and the mucosa.

From the above mentioned description it appears that the most serious advantage of the method is the manner of administration of the drug (external in combination with the lack of undesirable action in the suggested doses or/and the proposed pharmacotechnical forms) the relatively low cost and especially the most satisfactory result together with corresponding methods.

Amongst the probable methods of application,most advantageous is a synthesis in the gel form of relatively low viscosity which contains

0,3-0,9 % w/v misoprostol in the methylform of methylester and/or free acid,a complexforming means,as 1,6% w/v a-cyclodextrine and substances suitable for the formation of a gel e.g.hydroxypropyl methylcellulose "3000" 2% w/v,propylene glycol 10% v/v and Water to 100 ml. The gel contains 3-9 mg of active substance per ml.

Method of application:0.1(or more,depending on responce) are applied to the clitoris or/and to the vagina.

9 examples related to the pharmacotechnical forms and the ways of application of misorostol:

1)0,10 ml gel,relatively low viscosity containing 0,3-0,9% w/v misoprostol for applying to the clitoris or/and to the vagina.

Synthesis:

1-1.Misoprostol	0,3-0,9 g
Hydroxypropyl Methylcellulose "3000"	2 g
Water purified to	100 ml
1-2.Misoprostol	0,3-0,9 g
Sodium Carboxymethylcellulose	2 g
Propylene Glycol	25 ml
Water purified to	100 ml

2)0,10 ml gel of relatively high viscosity,containing 0,30-0,90% w/v in misoprostol for vaginal application.

Synthesis:

2-1.Misoprostol	0,30-0,90 g
Hydroxypropyl Methylcellulose "3000"	4 g
Water purified to	100 ml
2-2.Misoprostol	0,30-0,90 g
Sodium Carboxymethylcellulose	4 g
Propylene Glycol	25 ml
Water purified to	100 ml

3)0,10 ml of aqueous solution of misoprostol containing 0,3-0,9% w/v for clitoral or/and vaginal application.The solution can also contain propylene glycol or glycerol in the corresponding proportions (e.g.10%) to increase the viscosity of the solution.

4)0,10 ml of ointment or emulsion o/w containing 0,3-0,9% w/w in misoprostol for clitoral or/and vaginal application,where misoprostol is found spread in the continuous (aqueous) phase.

Synthesis:

4-1.Misoprostol	0,3-0,9 g
Vanishing Cream to	100 g

(Although for the requirements of this example as Vanishing Cream we used Bepanthéne® Cream of Roche,we have various creams o/w which are available in commerce or are described in National Pharmacopoeies and can be used for the same purpose).

5)Vaginal ovules of suitable dimensions,weight about 300-900 mg, containing 0,04-0,20% w/w misoprostol for vaginal use.

Synthesis:

5-1.Misoprostol	0,3-0,9 g
Glycerol	70 g
Gelatine	20 g
Water purified to	100 g

6)0,10 ml gel (or more depending of response) according to the examples (1-1) and (2-1) which contains moreover 1,6% w/v a-cyclodextrine.

7)0,10 ml gel (or more depending of response) according to the example (6) which contains moreover 10 ml ethyl alcohol 96° and 0,5 mg/ml alprostadil.

Notes:1)The incorporation of misoprostol in bases already mentioned took place in normal temperature (20-25°C) and at a temperature not exceeding 40°C.

2)No significant changes in misoprostol activity was observed as a function of pH,we observent however an important reduction or/and neutralization of misoprostol action in the presence of Polysorbate "80".

3)The time of appearance of the result varies from 20-40 minutes.The timing of the appearance and the intensity of the result seems to be able been positively influenced by certain moisturising agents (e.g.Propylene Glycol,Glycerol) as well as by certain substances which reinforce by various mechanisms the transcutaneous absorption (e.g.Urea,Acid Citric).

4)High once only doses of misoprostol (>1000 mcg to the clitoris or to the vagina) cause certain systematic undesirable effects as shudder,feeling of hard ship,excitement and diarrhea.The presence of a-cycodextrine reduces the undesirable effects and allows the application once only of higher doses without notable effect on the timing of its action but with positive effect on the intensity result and with prolonging of its duration.

5)The doses which are mentioned in the examples are only indicative since the intensity of the result depends,apart from the nature and the grade of the sexual dysfunction on other factors as e.g.the degree of moisturising of the underlying tissue,the physiological situation of the skin or the mucosa etc.As had already been mentioned, misoprostol is an extremely hydrophile molecule compared with other prostaglandins of E_1 series (e.g. with alprostadil which can be dissolved in alcohol but her solubility in water is only 8000 mcg/100 ml at 35°C).

This consists an important advantage:

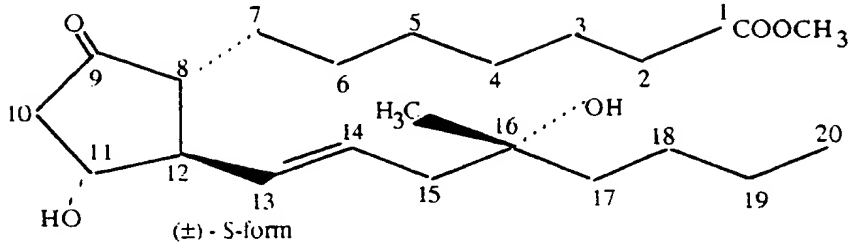
a)Because no use of organic factors is required (e.g.ethyl alcohol) which usually irritate tissues and are thus unsuitable for application on the skin and especially the mucus.

b)Because it allows the incorporation of active substances on a very small amount of excipient, suitable for application on surfaces of limited extent,as e.g.the clitoris.

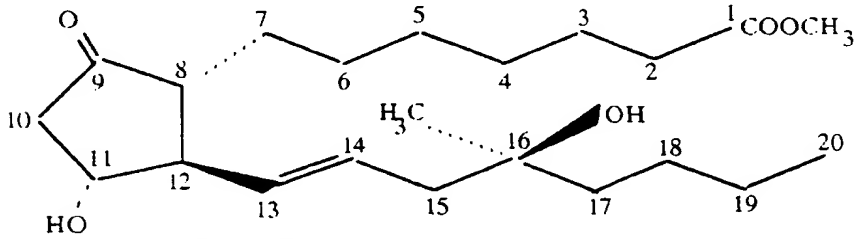
6)Misoprostol hasn't been accused for carcinogenic or teratogenic effect but because of the described irritation of the smooth uterine fibbers (Physicians Desc Reference,PDR,ed.Medical Economics Data,Production Company at Montrale 48th edition.1994,P.2197-2199), misoprostol must not becoming in touch with the genital system of the women who are pregnant.

STRUCTURAL FORMS

Fig. 1.Misoprostol

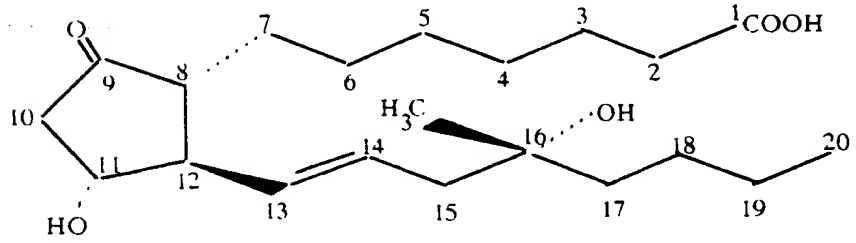


(±) - S-form

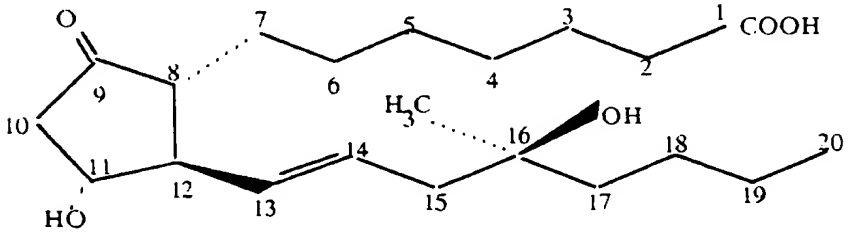


(±) - R- form

Fig. 2.Misoprostol acid



(±) - S- form



(±) - R - form

Claims

1)The use of misoprostol or/and its first metabolite, misoprostol acid,for the production of a drug applied topically to the clitoris or/and to the vagina and is destined for the therapy of sexual dysfunction in women due to vascular or other causes.

2)The use of misoprostol and/or its metabolite (misoprostol acid) according to claim (1) either as racemic mixtures or in the form of one of the stereoisomers from which they consist:[(±)-R form & (±)-S form].

3)The use of misoprostol and misoprostol acid according to claims (1) and (2) in the form of various galenic preparations (solutions,ointments,endourethral sticks,systems of controlled transdermal absorption) which,according to the general principles of pharmacotechnics, facilitate the application and precise administration of the right doses for the achievement of the desired therapeutical or diagnostic aim as described in claim (1).

4)The use of misoprostol and misoprostol acid according to claim (1),(2) and (3) in combination with other vasodilatory drugs as alprostadil for the appearance of synergistic action, as well as "passage accelerators" used normally in pharmaceutical technology aiming to increase absorption of drugs through the skin or the mucosa.

5)Use of misoprostol and misoprostol acid according to claim (1),(2) and (3) in combination with a-cyclodextrin or other substances which,according to the general methods used in pharmacotechny impedes or retards the appearance or undesired effects of the drug or prolong their pharmaceutical action.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GR 99/00030

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/557

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE PASCAL 'Online! INIST, CNRS (CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE), VANDOEUVRE-LES-NANCY, FR 96-0459457, 1996 MUNDLE ET AL: "vaginal misoprostol for induction of labor" XP002103712 abstract & MUNDLE ET AL: "vaginal misoprostol for induction of labor" OBSTETRICS AND GYNECOLOGY, vol. 88, no. 4, 1996, pages 521-525, -/—	1-5

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22 November 1999	03/12/1999

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INTERNATIONAL SEARCH REPORT

International Application No
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Date of the actual completion of the international search	Date of mailing of the international search report
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International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 23.05.2000
Applicant's or agent's file reference CF/G14817WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GR99/00030	13/08/1999	14/08/1998

Applicant
KAROUZAKIS, Petros et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	THORNTON, J Tel.+49 89 2399-8072

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
CF/G14817WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GR99/00030	13/08/1999	14/08/1998
International Patent Classification (IPC) or national classification and IPC		
A61K31/557		
Applicant		
KAROUZAKIS, Petros et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10/03/2000	23.05.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Trifilieff-Riolo, S Telephone No. +49 89 2399 7514

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GR99/00030

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-7 as originally filed

Claims, No.:

1-5 as originally filed

Drawings, sheets:

1/1 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-5.

because:

☒ the said international application, or the said claims Nos. 1-5 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-5
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-5
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	see separate sheet
	No:	Claims	

2. Citations and explanations

see separate sheet

The following document is cited:
D1: medline abstract 98376572, June 1998 of Eur. j. contracep. repro. health care, 3(2), June 1998

Section III:

Claims 1-5 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section V:

1. In view of the available prior art, the subject-matter of claims 1 to 5 is novel (A. 33(2)).

D1 describes the use of vaginal misoprostol to induce abortion. It does not contain any incentive to use that compound to remedy to female sexual dysfunction.
Therefore the requirements for inventive step are met (A. 33(3)).

2. For the assessment of the present claims 1-5 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.